UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/194,356	09/02/99	NERI	D 515-4132

HM12/0814

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
ARLINGTON COURTHOUSE PLAZA 1
2200 CLARENDON BLVD., SUITE 1400
ARLINGTON VA 22201-2601

EXAMINER	
HARRIS,A	
ART UNIT	**PAPER NUMBER**
1642	13

DATE MAILED: 08/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/194,356	Applicant(s) NERI ET AL.	
	Examiner Alana M. Harris, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *24-26 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23,27 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. It is noted that Applicant has submitted an improper preliminary amendment, which lacks indication of deleted and added matter to the claims. Notwithstanding, the amendment has been entered and the elected claims have been examined. Applicant is requested to review and comply with Rule 1.121 and respond accordingly.

Election/Restrictions

2. Applicant's election with traverse of Group I (claims 1-23, 27 and 29) in Paper No. 12 (filed May 24, 2001) is acknowledged. The traversal is on the ground(s) that the Examiner has not established an undue searching burden. This is not found persuasive. Groups I-IV are drawn to four different products made by different processes and Groups IV and V are processes that yield two different results. All of these groups require different searches.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-29 are pending.

Claims 6, 9-25 and 27-29 have been amended.

Claims 24-26 and 28 are drawn to non-elected claims.

Claims 1-23, 27 and 29 are examined on the merits.

Drawings

4. The drawings are objected to because of reasons cited on attached form PTO 948 completed by draftsman. Correction is required.

Claim Objections

5. Claim 6 is objected to because it suggests that claim 1 is a process claim and it is a product claim.

6. Claim 22 is objected to because it contains the word "aid" instead of "said".

7. Claim 5 is objected to under 37 CFR 1.75(c) as being in improper form because it depends on a multiple dependent claim (claim 3). See MPEP § 608.01(n).

Sequence Compliance

8. Claims 14-18 list amino acid sequences with no accompanying identifying SEQ. ID. Numbers. In order to fully comply with the sequence rules Applicants are required to insert SEQ. ID. Numbers.

Specification

9. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

10. The disclosure is objected to because of the following informalities: (a) there is text that is missing on page 2, between lines 28-32 and (b) there is no heading on page 20 referencing the brief description of the drawings. Applicants are requested to list "Brief Description of the Drawings" before line 11 on the aforementioned page.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-23, 27and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific binding members, single chain Fv molecules (CGS-1 and CGS-2), does not reasonably provide enablement for any specific binding member. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants have provided evidence in Examples 1 and 2 of the specification starting at page 22, line 9 showing that two human scFVS (CGS-1 and CGS-2) were isolated and found to bind specifically to the ED-B domain of human FN. Applicants' disclosure is only enabling for these two binding molecules. While Applicants' have defined a specific binding member at pages 6 and 7, it is clear that this is not an exhaustive lists that represents the plethora of binding members that would be capable of specifically binding the ED-B domain. A "specific binding member" could be anything,

such as a peptide, an organic molecule, an inorganic molecule, a DNA fragment, a carbohydrate, etc. Applicants' have not provided any guidance as to a conformation needed by the specific binding member for binding to the ED-B domain. Thus, undue experimentation would be required by one skilled in the art to search thousands upon thousands of compounds to determine which compounds would bind.

13. Claim 27 is rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claim 27 is drawn to the use of a specific binding member for the use in therapy. The specification while being enabling for a composition comprising scFV (CGS-1) and CGS-1, as well as control compositions and a pharmaceutically acceptable carrier, does not reasonably provide enablement for a "pharmaceutical composition" comprising these same components. Claims drawn to "pharmaceutical compositions" are broadly interpreted to read on compositions effective for use as *in vivo* therapeutics. In the absence of an established role of these scFvs in diseases it is impossible to predict what if any therapeutic effect the administration of these molecules would have for the treatment of cancers or in the broadly claimed "therapy". Applicants provide experimental data that suggest that scFv (CGS-1) is capable of targeting or localizing on a tumor (see page 38, lines 32-35 and Figure 5). There is no data or established

precedent presented that would lead one of skill in the art to believe that the tumor was obliterated or that there was arrested tumor growth.

The selection and development of such therapeutics is art known to be highly unpredictable. The specification exemplifies no examples of the effective use of the scFvs as a therapeutic pharmacological agent and no such uses are art known. The specification does not suggests what type of tumors or cancers that the "therapy" of claim 27 may encompass. This reasonably conjures the question as to how selective the use of the claimed composition clearly is or would be. Therefore, due to the unpredictability of therapeutics and the absence of any evidence concerning the effectiveness of the claimed pharmaceutical composition as a pharmacological agent, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use with a reasonable expectation of success, the invention commensurate in scope with this claim. There is no guidance as to how the instant molecules can be employed as therapeutic nor a basis to predict their efficacy in any therapy. Additionally, it would require undue experimentation of one skilled in the art to apply a method of treatment to a human based on the teachings of a method of treating a non-human animal. The applicant is advised to amend the claim to delete the recitation of "pharmaceutical" and specify the type of therapy designated for the use of a composition.

14. Claims 6, 9-23, 27 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **THIS IS A NEW MATTER REJECTION.** The recitation "isolated from synthetic molecular repertoires" in claim 6 is not supported by the claims or the rejection as originally filed.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 6-23, 27 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The recitation "synthetic molecular repertoires" in claim 6 is vague and indefinite. It is not clear what this type of repertoire is? Applicant is requested to clarify.

b. Claims 14-18 are vague and indefinite in the recitation "codon 1 [amino acid x]". A codon is a sequence of three adjacent nucleotides and not an amino acid. Applicants are requested to clarify the claims in which this recitation appears.

c. Claims 14-18 are vague and indefinite in the recitation "sequence derived from human germline DP47". Is not clear what type of sequence is derived from the germline. Nor is it clear whether or not this germline is a type of cell line or hybridoma.

d. The recitation "DP47" in claims 14-18 is vague and indefinite. It is not an art-recognized acronym. Applicants are requested to clarify the meaning of the acronym.

e. The phrase "an effective amount" in claim 23 is indefinite when the claims fails to state the function which is to be achieve. In re Frederiksen, 213 F 2d 547, 102 USPQ 35 (CCPA 1954).

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1-4, 6-9, 11-13, 19, 23, 27 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by European Patent Number 0 344 134 (November 29, 1989/Reference AM on IDS). European Patent # 0 344 134 discloses on page 2, lines 5 and 6 a specific monoclonal antibody to a protein sequence coded for by the exon ED-B of a human fibronection. It is art known that the ED-B domain is conserved amongst the human, mouse, rat and chicken species, hence the antibody of the European Patent inherently binds all of the said species. The epitope recognized by the antibody, which inherently comprised an antibody antigen binding domain was found in a variety of fetal, adult tumoral and normal tissues (see page 2, lines 21 and 22; Table I on page 3). This antibody was able to bind FN containing ED-B after treatment of the FN with the protease thermolysin (see page 2, lines 31-33 and the "Localization of the antigenic..." section on page 6). Likewise, the antibody bound the ED-B domain, hence inherently inhibiting binding to B-FN (see abstract). The patent did not indicate that the FN was treated with N-glycanase, consequently the said monoclonal antibody should bind to B-

FN. The ED-B oncofoetal domain of fibronectin antibody was isolated from a synthetic molecular repertoire as evidenced on page 5, lines 25-50. The disclosed specific binding member when measured, as a purified monomer would inherently have a dissociation constant (Kd) of 6 x 10^{-8}M or less.

As revealed on page 4, line 51- page 5, line 2 the patent disclosed a pharmaceutical composition comprising the antibody or specific binding member, as well as diagnostic kit suited to detect the presence of FN containing the ED-B sequence with said antibody. This monoclonal antibody by itself or bound cytotoxic or antitumor medicaments can be used for therapeutic purposes.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 1, 6, 20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over European Patent Number 0 344 134 (November 29, 1989/Reference AM on IDS), in view of Bird et al. (Science 242:423-242, 1988). The teachings of patent 0 344 134, of a specific binding member that is the same as that claimed has been discussed in the paragraphs above. The aforementioned reference does not teach that the antibody is single-chain Fv molecule (scFv) or a dimeric scFv.

However, Bird teaches the production of single-chain fragments, dimeric scFV and the efficacy of single-chain antibodies. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to produce single-chain antibodies. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in all references that single-chain antibodies are advantageous because of their small size, lower background in imaging applications, less immunogenic and ability to penetrate the microcirculation surrounding solid tumors better.

Conclusion

21. Claims 14-18 and 22 are free of the art.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703)306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703)308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703)308-4315 for regular communications and (703)308-4315 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

Alana M. Harris, Ph.D.
August 13, 2001

SHEELA HUFF
PRIMARY EXAMINER

Attachment for PTO-948 (Rev. 03/01, or earlier)
6/18/01

The below text replaces the pre-printed text under the heading, "Information on How to Effect Drawing Changes," on the back of the PTO-948 (Rev. 03/01, or earlier) form.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the Notice of Allowability. Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a).

Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.